Nutrition and prostate cancer

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Review

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Nutrition and Prostate Cancer

Abstract

Nutrition is apparently a major risk factor for the development and progression of prostate cancer. Based on experimental studies and epidemiologic data mainly from case-control studies or cohort studies, there is strong evidence that reduction of the total energy consumption, a diet comprising less than 30% fat, and increased intake of phytoestrogens, vitamins D and E and selenium could yield a decreased prostate cancer incidence. Furthermore, some of these measures appear to have antitumoral capacity even in the presence of the disease. These observations have provided a rationale to forward large prospective trials on dietary interventions to prove the efficacy of the concept and further delineate the correlation between nutritional compounds and prostate cancer risk. These chemoprevention trials are either aiming a reduction prostate cancer incidence or a decrease in tumor progression. Depending on the study design, large numbers of individuals need to be enrolled and long follow-up intervals are required thus making such trials highly complex and cost-intensive. However, regarding the potential relevance of chemoprevention on public health, further efforts to identify nutritional factors affecting prostate cancer growth are warranted.

Introduction

Epidemiologic studies have demonstrated that the incidence of clinically overt prostate cancer is about 10 times higher in White US American men as compared to Japanese men with a comparable socioeconomic background [1, 2]. Furthermore, migration studies showed that the low prostate cancer incidence in Japanese immigrants in the US rose about 3 times within one generation. Also in Europe there is a significant difference in prostate cancer incidence from 11.8/100,000 male population in Portugal to 50.2/100,000 males in Sweden.

Although prostate cancer is one of the most common cancers in western Countries, its etiology is mostly unknown. However, aside of age and ethnicity, several environmental factors, including diet, have been identified in epidemiological studies, although these findings have not been completely consistent [3–5]. So far, several nutritional compounds have been suggested to influence prostate cancer (table 1). Through the past decade the understanding of the molecular mechanisms potentially underlying these effects have been identified thus now providing the basis for interventional studies.

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Table 1. Nutritional compounds potentially involved in the development of prostate cancer

Phytoestrogens
Antioxidants (carotenoids, vitamins A, C, D, E)
Selenium
Fat/total energy uptake

Phytoestrogens

Testosterone is known to play a crucial role in the development and progression of benign and malignant prostatic disease. Although it remains a matter of discussion if testosterone serum levels are correlated with the incidence of prostate cancer [6–8], several observations suggest that free testosterone might be one of the factors inducing and stimulating prostate cancer. Phytoestrogens are known to be strong inhibitors of 5-α-reductase thus potentially counteracting testosterone-mediated stimulation of prostatic growth [9, 10].

There is some epidemiologic evidence that phytoestrogens may influence progression of benign and malignant prostatic disease [5, 11, 12]. Diets in areas with a low prostate cancer incidence (far-east Asia, southern Europe) are rich in fibers and vegetables containing high amounts of isoflavonoids, flavonoids and lignans, the most important categories of phytoestrogens. While high concentration of flavonoids and isoflavonoids, e.g. daidzein or genistein, are detected in vegetables (e.g. soy) and fruits, lignans can also be found at high concentrations in linseeds, grains and cereals. Phytoestrogens may influence growth and proliferation of prostate cells through different mechanisms (table 2). As expected, serum levels or urinary concentrations of phytoestrogen metabolites are much higher in men from areas with low prostate cancer incidence as compared to men from western countries [11–13].

Despite experimental and epidemiologic evidence from ecological studies on the beneficial effects of phytoestrogens, only few data from case-control and cohort studies have been published so far. Two case-control studies report a significant inverse correlation between phytoestrogen intake and prostate cancer risk [14, 15]. These observations are further supported by the summarized data from three case-control studies including 617 prostate cancer cases from Canada [16]. The intake of green vegetables, beans, lentils, nuts and cruciferous vegetables was inversely correlated with the incidence of prostate cancer.

Table 2. Putative mechanisms of phytoestrogen action on prostate cells

Increase of SHBG serum concentration and subsequent decrease of free testosterone through binding to liver estrogen receptors
Decrease of DNA synthesis through inhibition of tyrosine kinase and topoisomerase
Decrease of the effects of free radicals through antioxidant properties
Inhibition of cytochrome P450 activation
Neoangiogenesis inhibition
Inhibition of intraprostatic testosterone metabolism through inhibition of 5α-reductase and aromatase

Similar results were obtained in two cohort studies from the US, both showing significant beneficial effects of soybean product consumption on prostate cancer risk [17, 18]. However, despite these encouraging data, the assessment of dietary phytoestrogen consumption is highly complex and the results of these trials may be confounded by multiple parameters [19]. Therefore, further assessment of this topic is required.

Lycopene

Lycopene is a carotenoid that is present in tomatoes, processed tomato products and several fruits. It is one of the most potent antioxidants among dietary carotenoids. Dietary intake of tomatoes and tomato products has been shown to be associated with a decreased risk of chronic diseases [20]. Although the antioxidant properties of lycopene are thought to be primarily responsible for its effects, evidence is accumulating that other mechanisms may also be involved.

The effects of lycopene on prostate cancer have been extensively addressed in a variety of studies. While case-control studies by Le Marchand et al. [21], Key et al. [22] and Hayes et al. [23] showed no differences between those individuals on a lycopene-rich diet and the controls, the trials by Norrish et al. [24] and Tzonou et al. [25] yielded a decreased risk of developing prostate cancer for individuals consuming high amounts of tomatoes or having a lycopene-rich diet reaching significance only in the latter trial (table 3).

Furthermore, the impact of lycopene on prostate cancer risk has also been studied in several cohort studies [26–31] (table 3). All trials studying the effects of tomato-rich diets showed a significant decrease of the

Table 3. Summary of trials investigating the influence of lycopene and tomatoes/tomato products on the incidence of prostate cancer

Reference	Cases	Measure	Ass.	RR/OR (95% CI)[1]
Case-control trials				
Le Marchand (1991) [21]	452	Diet	NS	0.9 <70 years
			NS	1.1 ≥70 years
Key (1997) [22]	328	Diet	NS	0.99 (0.68–1.45)
Tzonou (1997) [25]	320	Tomatoes	↓	0.70
Hayes (1999) [23]	932	Diet	NS	
Norrish (2000) [24]	317	Diet	NS	0.76 (0.50–1.17)
Cohort studies or nested case-control studies				
Mills (1989) [26]	180	Tomatoes	↓	0.60 (0.37–0.97)
Hsing (1990) [27]	103	Serum	NS	0.50 (0.20–1.29)
Giovannucci (1995) [28]	773	Tomato products	↓	0.65 (0.44–0.95)
Nomura (1997) [29]	142	Serum	NS	1.1 (0.5–2.2)
Cerhan (1997) [30]	1,050	Tomatoes	↓	0.5 (0.3–0.9)
Gann (1998) [31]	578	Plasma	↓	0.56 (0.34–0.92)

NS = Statistically not significant; ↓ = statistically significant inverse association.
[1] Comparing extreme categories, low = reference.

prostate cancer risk in individuals with a high consumption of tomatoes or tomato products [26, 28, 30]. However, it remains unclear if these beneficial effects are related to lycopene intake or rather to the multiple other nutritional compounds in tomatoes.

In three other trials, lycopene serum or plasma levels were studied [27, 29, 31]. While Nomura et al. [29] did not find a difference between the study groups, Gann et al. [31] showed a correlation with a significant decrease of the prostate cancer risk in the group with high lycopene plasma levels. A similar decrease was also seen by Hsing et al. [27], however, because of the small number of prostate cancer cases (n = 103), this observation was not significant.

In a recent review on 72 studies concerning the impact of tomatoes and tomato-based products on the incidence of various cancers, Giovannucci [32] identified 35 trials reporting a significant inverse relationship. The evidence for a benefit was strongest for cancers of the prostate, lung and stomach. Moreover, no study indicated that higher tomato consumption or lycopene blood levels statistically significantly increased the risk of cancer of any site.

Vitamins

From epidemiologic evaluations there is a great body of evidence of an inverse correlation between the intake of vitamins and the incidence of different types of cancer. These observations are further supported by results of experimental trials. Specifically with regard to the development of prostate cancer, vitamins A, C, D and E have been suggested to be of relevance.

The molecular pathways through which vitamins may act are severalfold. Neutralization of the oxidative capacity of free radicals in the tissue appears to be a major way of action for several vitamins [33]. Furthermore, stimulation of the immune system and its putative antitumoral actions has been shown to be mediated through vitamins. Retinoids and vitamin A are known to be strong inducers of cellular differentiation. Within this context the loss of intercellular interaction, another aspect of dedifferentiation, can be restored under the influence of vitamins. Apart from these indirect actions, direct antiproliferative effects of several vitamins in vitro and in vivo have been reported [33–38].

Total Vitamin A (β-Carotene and Retinol)

There is some experimental evidence that the provitamins or vitamin A may influence the development and progression of prostate cancer. Williams et al. [38] demonstrated an in vitro down-regulation of the proliferation of prostate cancer cells in the presence of β-carotene. Further investigation suggests a metabolic conversion of β-carotene to retinol by the prostate tumor cells. This observation supports the results of a

Table 4. Summary of trials investigating the influence of vitamin C on the incidence or mortality of prostate cancer

Reference	Cases	Measure	Ass.	RR/OR (95% CI)[1]
Case-control				
Vlajinac (1997) [56]	101	Diet	NS	0.90 (0.48–1.69)
Deneo-Pelegrini (1997) [52]	175	Diet	↓	0.4 (0.2–0.8)
Kristal (1999) [57]	697	Suppl.	NS	0.77 (0.57–1.04)
Cohort studies				
Daviglus (1996) [50]	132	Diet	NS	1.03 (0.59–1.6)
Eichholzer (1999) [54]	30	Plasma	NS	0.93 (0.31–2.78)[2]

NS = Statistically not significant; ↓ = statistically significant inverse association.
[1]Comparing extreme categories, low = reference; [2]high = reference.

case-control study in Japan which showed that consumption of vegetables containing >600 μg carotin/100 g was associated with a decreased prostate cancer risk [39, 40]. An inverse correlation between higher carotene intake and prostate cancer risk was also observed in a case-control study in England [19]. These findings contrast to the results obtained in a recent case-control study by Norrish et al. [24] and in the Lutheran Brotherhood Cohort Study [41].

Most notable, the effects of β-carotene on prostate cancer risk have also been addressed in large interventional studies. The CARET trial (30 mg β-carotene/day) and the Physicians' Health Study (PHS) I (50 mg β-carotene every second day) could not demonstrate a beneficial effect of β-carotene on prostate cancer incidence [42–44]. However, in the PHS I trial those individuals with initial low plasma levels of β-carotene had a statistically significant 32% risk reduction after subsequent β-carotene supplementation as compared to those individuals not receiving β-carotene [43]. This contrast to a nonsignificant 33% increase in prostate cancer incidence in the individuals with high pre-study β-carotene plasma levels.

These findings could explain the observations made in the ATBC interventional trial including 29,133 male smokers aged 50–69 years, where the treatment group received 20 mg β-carotene/day alone or in combination with α-tocopherol (50 mg) [45–48]. In this group an increased incidence (23%) and mortality (15%) from prostate cancer was observed. Since no pre-study examination of the plasma levels was performed, a possible interaction of low or high β-carotene levels could not be disclosed.

In summary, the effects of β-carotene or total vitamin A on the development of prostate cancer remain inconclusive. There is even some evidence that uncontrolled β-carotene intake could be hazardous. However, so far, it appears that supplementation of β-carotene could be beneficial in a distinct group of men with low β-carotene plasma levels.

Vitamin C

The influence of vitamin C on prostate cancer has been studied in a number of case-control studies and cohort trials [49–57] (table 4). In the majority of these studies no evidence of an inverse association between vitamin C intake or vitamin C plasma concentrations on the incidence or mortality of prostate cancer was noted. A borderline significant inverse association was observed with daily supplemented use only in the case-control study by Kristal et al. [57]. It was suggested that higher than dietary amounts of vitamin C might be necessary for a protective effect. Although the results of prospective interventional trials are not yet available, it appears unlikely that vitamin C may play a major role in prostate cancer prevention.

Vitamin D

Vitamin D plays a crucial role in osseous metabolism and vitamin D deficiency or vitamin D receptor disorders are correlated with osteomalacia. Furthermore, it has been speculated that decreased vitamin D serum levels could be responsible for the increased risk in Black US citizens developing prostate cancer. Peehl et al. [35, 36] studied the antiproliferative effects of vitamin D_3 in primary cultures of prostatic tissues derived from prostate cancer patients. The antiproliferative effects of vitamin D_3 were more pronounced in prostate cancer cells as compared to prostate fibroblasts. A decreased expression of vitamin D receptors in fibroblasts was suggested to be responsible for this observation. Further investigation of the mechanism

Table 5. Summary of trials investigating the influence of serum vitamin D and calcium intake on the incidence of prostate cancer

Reference	Cases	Measure	Ass.	RR/OR (95% CI)[1]
Case-control				
Vlajinac (1997) [56]	101	Dietary calcium	↓	0.37 (0.14–0.99)
Chan (1998) [58, 59]	526	Dietary calcium	↑	1.9 (1.2–3.0)
Kristal (1999) [57]	697	Suppl. dietary calcium	NS	1.04 (0.61–1.78)
Ahonen (2000) [60]	149	Serum (vitamin D)	↓	1.7
Cohort studies or nested case-control studies				
Nomura (1988) [61]	136	Serum	NS	1.0 (0.5–2.1)
Giovannucci (1998) [63]	423	Diet (calcium intake)	↑	2.97 (1.6–5.5)
Schuurman (1999) [64]	642	Diet (calcium intake)	NS	n.r.

NS = Statistically not significant; ↓ = Statistically significant inverse association; ↑ = statistically significant direct association.
[1] Comparing extreme categories, low = reference; n.r. = not reported.

underlying the antiproliferative effects showed that growth inhibition was mediated both by androgen-dependent and androgen-independent pathways [37].

The relation between the intake of dairy products and prostate cancer risk has been investigated in a population-based case-control study by Chan et al. [58]. The investigation of 526 cases and 536 controls showed calcium intake to be an independent predictor of prostate cancer, and specifically for metastatic tumors. Since calcium consumption is supposed to lower vitamin D serum levels, the correlation between vitamin D metabolite serum levels and prostate cancer was studied in a nested case-control study in a Japanese-American population including 136 cases and 136 matched controls [61]. No difference between vitamin D serum levels in the two groups was observed. However, individuals with low vitamin D serum levels were underrepresented which may hide an existing difference (table 5).

The investigation of stored sera collected from over 250,000 individuals through the years 1964–1971 showed significantly lower vitamin D serum levels in older patients (>57 years) with prostate cancer as compared to controls without prostate cancer [62]. Similarly, Ahonen et al. [60] reported a correlation between low vitamin D serum levels and subsequent development of prostate cancer in a Finnish study including 19,000 healthy men. However, in this trial low vitamin D serum levels were specifically linked to aggressive tumors in younger patients.

Other studies aiming at the relation between vitamin D receptor polymorphism and prostate cancer risk yielded controversial results. While a heterozygosity or homozygosity for the absence of the Bsm I restriction site was associated with significant decrease of the prostate cancer risk in a Japanese population [65], this finding was not confirmed in a case-control study nested in the Physicians' Health Study [66].

So far, only phase I/II trials on a therapeutical use of vitamin D have been published. Gross et al. [67] demonstrated a significant decrease of serum PSA in 6 of 7 patients with early recurrent prostate cancer receiving 0.5–2.5 μg vitamin D_3/day for 6–15 months. Van Veldhuizen et al. [68] investigated vitamin D replacement therapy in patients with hormone-refractory metastatic prostate cancer. Four of the 16 patients had improvements in pain scores and 6 patients had improved muscle strength measurements. Notably, 7 of the 16 patients had decreased baseline vitamin D levels.

In summary, the role of vitamin D deficiency in the development of prostate cancer remains controversial. Despite the influence of high-dose vitamin D treatment on serum PSA, more detailed analyses are required to accept this approach as a viable therapeutic option.

Vitamine E (α-Tocopherol)

Vitamin E is a potent intracellular antioxidant with demonstrable antitumoral properties in several cancer models including sarcomas and gastrointestinal tumors [69–71]. It has been hypothesized that the antioxidant properties of vitamin E may reduce the dietary fat-induced oxidative stress and thus subsequently affect tumor cell growth.

Based on these investigations and further epidemiologic evidence that vitamin E could also have a preventive effect in prostate cancer, this question has been addressed in more detail in a variety of epidemiologi-

Table 6. Summary of trials investigating the influence of vitamin E on the incidence or mortality of prostate cancer

Reference	Cases	Measure	Ass.	RR/OR (95% CI)[1]
Case-control				
Rohan (1995) [53]	207	Diet	NS	n.r.
Andersson (1996) [72]	526	Diet	NS	0.91 (0.64–1.28)
Vlajinac (1997) [56]	101	Diet	↓	0.15 (0.05–0.53)
Deneo-Pelegrini (1999) [52]	175	Diet	↓ ptrend	0.6 (0.3–1.1)
Hayes (1999) [23]	932	Diet	NS	n.r.[2]
Tzonou (1999) [25]	320	Diet	↓	0.53 (0.30–0.94)
Kristal (1999) [57]	697	Suppl.	NS	0.76 (0.54–1.08)
Cohort studies or nested case-control studies				
Knekt (1988) [73]	26	Serum	NS	0.42 (0.10–1.71)
Hsing (1990) [41]	103	Serum	NS	1.00 (0.37–2.68)
Nomura (1997) [29]	142	Serum	NS	0.9 (0.7–2.9)
Chan (1999/2000) [58, 59]	1,896	Suppl.	NS	1.07 (0.95–1.20)
Gann (1999) [31]	578	Plasma	NS	0.64 (0.38–1.07)
Eichholzer (1999) [54]	30	Plasma	NS	0.76 (0.25–2.37)[2]

NS = Statistically not significant; ↓ = statistically significant inverse association.
[1] Comparing extreme categories, low = reference; [2]high = reference; n.r. = not reported.

Table 7. Summary of trials investigating the influence of vitamin E on the incidence and mortality of prostate cancer in smokers

Reference	Cases	Measure	Ass.	RR/OR (95% CI)[1]
Cohort studies or nested case-control studies				
Knekt (1988) [73]	115[2]	Serum	NS	0.74 (0.44–1.26)
Chan (1999) [74]	55	Suppl.	↓	0.47 (0.24–0.92)
Gann (1999) [31]	578	Plasma	↓	0.51 (0.26–0.98)
Eichholzer (1999) [54]	30	Plasma	↓	3.26 (1.27–8.35)[2]
Interventional studies				
ATBC [45–48]	62	50 mg	↓	0.59 (0.35–0.99)

NS = Statistically not significant; ↓ = statistically significant inverse association.
[1] Comparing extreme categories, low = reference; [2] High = reference.

cal studies (table 6). However, although several case-control studies provided some evidence for a decreased incidence of prostate cancer in populations consuming a vitamin E-rich diet, this finding was not confirmed in subsequent cohort studies [5, 45–48].

Stratification for several risk factors in the Basel Cohort Study, however, showed that smokers with low vitamin E plasma levels had a significantly increased risk of prostate cancer mortality [54]. Reanalysis of the respective data from several other studies were mostly in concordance with this finding (table 7). In the ATBC interventional trial this hypothesis could be confirmed [45, 47]. Subjects receiving α-tocopherol (50 mg daily) for 5–8 years had a 32% decrease in the incidence and a 41% reduction in mortality from prostate cancer.

In summary, results of epidemiological studies do not support a general protective effect of vitamin E against prostate cancer. However, results of four distinct populations, the US physicians' study, the Finnish ATBC trial, the Swiss Basel Study and the US health professionals' blood investigations, suggest that vitamin E may provide benefits against advanced prostate cancer or prostate cancer mortality among smokers or recent ex-smokers, but not among nonsmokers [31, 45–48, 54, 74].

Selenium

The inhibitory effect of selenomethionine, the predominant from of selenium in dietary supplements on the growth of prostate cancer cells and other tumor cell lines in vitro, has recently been studied by Redman et al. [75]. They found tumor cells to be approximately

Table 8. Summary of trials investigating the influence of dietary fat on the incidence of prostate cancer

Reference	Cases	Ass.	RR/OR (95% CI)
Case-control studies			
West (1991) [51]	679	↑	2.9 (1.08–8.4)
Ghadirian (1996) [83]	232	NS	n.r.
Vlajinac (1997) [56]	101	↑	3.6 (1.0–12.8)
Meyer (1997) [84–86]	215	↑	2.67 (??)
Lee (1998) [87]	133	↑	3.6 (1.8–7.2)
Deneo-Pelegrini (1999) [52]	175	↑Trend	1.8 (0.9–3.4)
Tzonou (1999) [25]	320	↑	n.r.
Ramon (2000) [55]	217	↑	2.0 (1.2–3.2)
Cohort studies or nested case-control studies			
Severson (1989) [17]	174	NS	0.91 (0.64–1.28)
Veierod (1997) [88]	72	NS	1.3 (0.6–2.8)
LeMarchand (1994) [89]	198	↑	1.6 (1.0–2.4)
Hayes (1999) [23]	932		
Total PCA		NS/↑[2]	1.1–2.1
Advanced PCA		↑/↑[2]	2.2–4.2
Schuurman (1999) [90]	642	NS	1.1

NS = Statistically not significant; ↑ = statistically significant direct association.
[1] Comparing extreme categories, low = reference; n.r. = not reported.
[2] White/Black US citizens.

1,000 times more sensitive as compared to normal diploid fibroblasts.

These observations match with data from a longitudinal case-control study on 111 subjects developing cancer within 5 years after obtaining blood samples for determination of serum selenium levels and compared the results with the levels of 210 control individuals not developing cancer within the same period [76]. The mean selenium levels of the cancer patients was significantly lower as compared with the controls. A similar study design was chosen in a prospective case-control study by Criqui et al. [77]. Baseline levels of plasma selenium, retinol and retinol-binding protein were compared in 136 case patients who subsequently died from cancer and 238 matched controls. Serum selenium was lower in case patients with gastrointestinal or prostate cancer, however, without reaching significance.

Hardell et al. [78] reported on a case-control study comparing selenium plasma levels from 164 patients with prostate cancer with 152 patients with benign prostatic hyperplasia. In those patients not taking supplementary selenium, the selenium levels were significantly lower in the cancer patients as compared to the controls. Yoshizawa et al. [79] conducted a nested case-control study within a large cohort study including 51,529 health professionals. Selenium levels were determined in toenail clippings. After controlling for several potentially interfering factors, higher selenium intake was found to be associated with a reduced risk for advanced prostate cancer.

For those patients enrolled in the ATBC study, baseline levels for several parameters were obtained [48]. No significant differences were reported for the incidence of prostate cancer and serum selenium levels. In an another interventional trial, Combs et al. [80] randomized 1,312 patients with a history of basal/squamous cell carcinoma in a double-blind fashion to either receive 200 μg selenium/day or placebo. While recurrence of skin cancer was not significantly reduced, total mortality and cancer mortality from all cancers, and in particular incidence and mortality from prostate cancer (secondary endpoints of the trial), were significantly reduced [81].

Dietary Fat

A high-fat diet has frequently been associated with an increased risk of prostate cancer. This aspect has been studied in in-vivo experiments where the growth of LNCaP cells in nude mice was investigated. Tumor

growth and serum PSA were significantly decreased in those animals receiving a low-fat diet as compared to control mice receiving an isocaloric high-fat diet [5].

Several aspects of increased fat intake, i.e. high serum cholesterol, total fat intake, the intake of saturated or unsaturated fatty acids or animal fat consumption have been studied in a variety of case-control or cohort studies (table 8). In a recent review addressing this topic, 11 out of 14 case-control trials yielded a significant correlation between fat consumption and prostate cancer risk [5]. Furthermore, 4 of the 5 cohort studies cited including nearly 100,000 individuals reported a relative risk ranging from 1.8 to 2.4 for people with high-fat intake. Even a correlation between fat consumption and high-grade/high-stage prostate cancer and prostate cancer mortality has been suggested by several studies [5, 82]. Meyer et al. [84–86] showed that a high intake of saturated fatty acids in patients with prostate cancer was significantly associated with tumor progression and mortality. In contrast to most earlier studies, these data were adjusted for total calorie intake.

These observations are further supported by studies reporting a correlation between overweight (body mass index) and the prostate cancer risk [5, 30, 91, 92]. In contrast to the obvious-tumor-promoting effects of saturated fats especially from animal sources, the intake of fat derived from plants or ω-3 fatty acid appears not relate to an increased risk developing prostate cancer [5, 93, 94].

Conclusions

Large autopsy studies suggest that the incidence latent prostate cancer is similar worldwide. This observation contrasts to the regionally different incidence of overt or clinically relevant tumors. Therefore, already a long time ago an environmental influence on the progression of microscopic to clinically relevant prostate cancer was postulated. This hypothesis was supported by migration studies demonstrating the increase of prostate cancer incidence in populations moving from areas with a low incidence in the Far East to areas with high incidence in the US [1, 2].

Throughout the last two decades a significant number of studies on the impact of nutritional compounds on the development but also on the course of disease of prostate cancer have been published. Considering the general question regarding an effect of nutrition on prostate cancer there is – despite several contradictory reports – increasing evidence supporting this hypothesis [95]. However, when it comes to more detailed questions aiming at the nature of relevant nutritional compounds, instead of clear conclusions more and more open questions remain.

Table 9. Factors influencing the result of trials investigating the impact of nutrition on prostate cancer

Validity of studies (case-control, cohort studies, interventional trials)
Problem of follow-up interval in the interventional and most cohort studies
Reliability of questionnaires
Hereditary factors
Data from different ethnical populations
Correlation between nutrition and lifestyle
Interaction between several nutritional compounds

These contradictory observations are better understood in the light of the complexity of the problem. So far, multiple factors potentially influencing the results of the respective trials have been identified (table 9).

Hypotheses of actual trials are frequently based upon results obtained in studies of questionable quality. Most results discussed in numerous review articles on this topic have been obtained by case-control studies. However, the validity of this type of trial is limited since selection bias is immanent and may be responsible for conflicting results [96]. In contrast, the impact of cohort studies is certainly superior, but high costs and long follow-up intervals required in general represent significant obstacles to launch this type of study. The most valuable information can be obtained through interventional trials, however until today only very few trials of this type have been generated to study the role of nutrition on prostate cancer [42–48, 97].

The validity of questionnaires is another problem that may distort the results of those trials relaying on self-reports of individuals. An investigation on the reliability of self-reports demonstrated a high level of inaccuracy specifically if non-life-threatening issues were assessed [98–100]. This has led to the inclusion of objective parameters through the analysis of serum, tissue, saliva and toenails in more recent trials [81, 101, 102].

Furthermore, the fact that hereditary factors also affect the results of epidemiologic studies on prostate cancer [103] and, furthermore, that data from different

ethnical populations yield different results further impedes the interpretation of the reports [104]. However, even within ethnically homogeneous populations, the correlation between nutrition and life-style may be confounded by genetic factors. Cross-national (meta)-analyses could be one option to address this problem but the quality of the different trials included in this type of study is hard to control for [105].

Apart from these factors that could be theroretically taken into account designing a trial on nutrition in prostate cancer, the interaction between the different nutritional compounds remains a key problem in population-based trials. Considering the putative beneficial effects of tomatoes and tomato products, it is nearly impossible to identify which of the multiple compounds or which combination of compounds may be responsible for beneficial effects. And even the administration of a single compound – e.g. a vitamin – may be influenced by other interacting nutritional or lifestyle factors.

However, these problems should not discourage the scientific community to conduct further well-designed trials on this import issue but should caution inadequate expectations and overinterpretation of the results of single trials. Today the concept of an impact of nutrition on prostate cancer appears well established but the details still require further characterization. Primary and secondary as well as tertiary prevention need to be addressed [97]. Considering the noninvasiveness of this approach and the putative benefits, a thorough investigation of this issue appears worthwhile and certainly justifies the efforts invested in this topic worldwide [97, 106, 107].

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